UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,410	12/19/2001	Yves Dubaquie	P1712R1-1D1	4233

25213 7590 07/18/2003

HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/18/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	10/028,410	DUBAQUIE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- Th MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-14* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-7, drawn to a method for treating a disorder characterized by dysregulation of the GH/IGF axis in a mammal in Paper No. 11 (25 April 2003) is acknowledged. The traversal is on the ground(s) that since claims 1-14, whether method or kit, all relate to the treatment of disorders characterized by dysregulation of the GH/IGF axis, they should all be classified in class 514, subclass 2, and examined together in one application. This is not found persuasive because Groups I and II are related as product and process of use. The claimed IGF-I variant can be used in materially different processes, such as diagnostic assays, polypeptide purification, or as an antigen for the production of antibodies. Furthermore, the inventions of Groups I and II require a divergent literature search, with no reason to believe that the searches would be co-extensive.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11 (25 April 2003).

Claims 1-7 are under consideration in the instant application.

Specification

1. The disclosure is objected to because of the following informalities:

1a. An updated status of the parent nonprovisional application should be included in the first sentence of the specification. A statement reading "This is a divisional of U.S. Application No. 09/477,924, filed January 5, 2000, Patent No. 6,403,764..." should be entered.

1b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD OF TREATING A DISORDER CHARACTERIZED BY DYSREGULATION OF THE GH/IGF AXIS BY ADMINISTRATION AN IGF-I VARIANT".

Appropriate correction is required.

Claim Objections

2. Claim 4 is objected to because of the following informalities: There are numerous spaces before the term "chronic" in the first line of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-7 are directed to a method for treating a disorder characterized by dysregulation of the GH/IGF axis in a mammal comprising administering to the mammal an effective amount of an IGF-I variant wherein the amino acid residue at position 16, 25, or 49 or the amino acid residues at positions 3 and 49 of native-sequence human IGF-I are replaced with an alanine, a

glycine, or serine residue. The claims also recite numerous disorders, including renal disorders. The claims recite further administering to the mammal an effective amount of a renally-active molecule. The claims recite that the mammal is a human and wherein both amino acid residues are replaced with alanine residues.

The specification teaches that the accumulation of active IGF molecules in the kidney could potentially be beneficial in chronic or acute renal failure. The specification also discloses that these conditions are characterized by abnormally high levels of IGFBP-1 and IGFBP-2, combined with a reduction of IGF-I synthesis (pg 41, lines 25-27). The specification teaches that IGF-I variants, F49A and E3A/F49A, are radiolabeled and administered intravenously to rats (pg 41, lines 28-29). The specification teaches that both IGF-I variants are cleared faster from the blood than wild-type human IGF-I and that the double mutant (E3A/F49A) cleared faster than the single mutant (F49A) (pg 41, lines 29-33; Figure 10A). The specification discloses that the majority of radioactively-labeled IGF molecules are detected in the kidney (pg 41, lines 33-37; Figure 10B). However, the specification does not teach treating a disorder characterized by dysregulation of the GH/IGF axis in a mammal by administration of any IGF-I variant. Undue experimentation would be required of the skilled artisan to determine the optimal quantity, duration, and route of administration of an IGF-I variant wherein the amino acid residue at position 16, 25, or 49 or the amino acid residues at positions 3 and 49 of native-sequence human IGF-I are replaced with an alanine, a glycine, or serine residue.

The phrase "disorder characterized by dysregulation of the GH/IGF axis" in the claims is interpreted by the Examiner to be broad, in that it encompasses any and all diseases or disorders involved in the regulation of anabolic and metabolic homeostasis (specification pg 11, lines 23-

25). The specification even discloses that examples of such diseases include renal disorders, congestive heart failure, poor nutrition, Turner's syndrome, Down's syndrome, hepatic failure, among others (pg 11, lines 28-32). These various diseases and disorders disclosed in the specification have different pathophysiologies. For example, one type of renal disorder, acute renal failure, is the rapid breakdown of renal function that occurs when high levels of uremic toxins accumulate in the blood. Acute renal failure occurs when the kidneys are unable to excrete the daily load of toxins in the urine (Singri et al. J Am Med Assoc 289(6): 747-751, 2003; pg 747). Down's syndrome is the most frequent form of mental retardation caused by a triplicate state (trisomy) of all or a critical portion of chromosome 21. A few of the major characteristics of Down's syndrome include mental retardation, ocular anomalies, skeletal anomalies, congenital defects (see Appendix A; http://www.emedicine.com/derm/topic687.htm#section~clinical). Additionally, congestive heart failure is a condition in which the heart can't pump enough blood to the body's organs. Congestive heart failure is an imbalance in starling forces or an imbalance in the degree of end-diastolic fiber stretch proportional to the systolic mechanical work expended in a contraction (Appendix B; http://www.emedicine.com/emerg/topic108.htm). Therefore, undue experimentation would be required of the skilled artisan to administer an IGF-I variant to individuals with all possible disorders or diseases of dysregulation of the GH/IGF axis and successfully treat the disorder or disease. One skilled in the art would also not be able to predict from the of the instant specification that an IGF-I variant recited in the claims would be able to treat all possible GH/IGF dysregulation disorders and diseases, such as acute renal failure, Down's syndrome, and congestive heart failure, because these diseases have different

pathophysiologies. Additionally, the claims do not specify what specific effect the "effective amount" of an IGF-I variant has. Undue experimentation would be required of the skilled artisan to determine the effect of an IGF-I variant after administration to a subject.

Due to the large quantity of experimentation necessary to treat all possible disorders characterized by dysregulation of the GH/IGF axis by administration of an IGF-I variant and to determine what effect an "effective amount" of an IGF-I variant has, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of administration of an IGF-I variant for all disorders characterized by dysregulation of the GH/IGF axis (see discussion), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Regarding claims 1-7, the acronyms "IGF-I, GH/IGF, and IGFBP-1" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

7. The term "renally-active molecule" in claim 5 is a relative term which renders the claims indefinite. The term "renally active molecule" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art

would not be reasonably apprised of the scope of the invention. Although the specification discloses a brief definition of a "renally-active molecule" on pg 13, lines 15-16, it remains unclear what type of molecule this is. For example, is the molecule a protein? DNA? An organic compound?

8. Claim 7 recites the limitation "both amino acid residues of the variant" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Dubaquie et al. Endocrinol 141(1) : 165-173, 2001.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
July 8, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER

Appendix A

Down Syndrome

Rate this Article
Email to a Colleague

Last Updated: May 9, 2002

Synonyms and related keywords: trisomy 21 syndrome, mongolism, congenital acromicria syndrome

AUTHOR INFORMATION

Section 1 of 11 Next

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Pictures Bibliography

Author: **Assen L Dourmishev, MD, PhD, DSc**, Professor, Department of Dermatology and Venereology, Medical University, Sofia, Bulgaria; Head, Department of Oncodermatology and Autoimmune Skin Diseases, Alexander's University Hospital, Sofia, Bulgaria

Coauthor(s): **Camila K Janniger, MD**, Chief of Pediatric and Geriatric Dermatology, Clinical Professor, Dermatology and Clinical Associate Profesor, Pediatrics, UMDNJ-New Jersey Medical School

Assen L Dourmishev, MD, PhD, DSc, is a member of the following medical societies: American Academy of Dermatology

Editor(s): **Albert C Yan, MD**, Assistant Professor, Department of Pediatrics, Section of Dermatology, Children's Hospital of Philadelphia and University of Pennsylvania; **Michael J Wells, MD**, Staff Physician, Department of Dermatology, Texas Tech University Health Sciences Center; **Robert A Schwartz, MD, MPH**, Professor and Head, Dermatology, Professor of Pathology, Pediatrics, Medicine, and Preventive Medicine and Community Health, UMDNJ-New Jersey Medical School; **Joel M Gelfand, MD, MSCE**, Instructor, Department of Dermatology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Hospital; and **Dirk M Elston, MD**, Consulting Staff, Department of Dermatology, Geisinger Medical Center

INTRODUCTION

Section 2 of 11 Back Top Next

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Pictures Bibliography

Background: Down syndrome is a frequent form of mental retardation associated with

Quick Find

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Pictures Bibliography

Click for related images.

Related Articles

Continuing Education

CME available for this topic. Click here to take this CME.

Patient Education

Click here for patient education.

characteristic morphologic features (mongolism) and many somatic abnormalities due to number of chromosomal aberrations.

The characteristic clinical features that discriminate the syndrome from other mental deficiencies were described first by John Langdon Down in 1866. It has typical physical features and multisystem anomalies, some of which are dermatologic. The skin lesions in this syndrome are noted by Seguin (1846), who spoke of *d'idiots furfuraces.* Certain dermatoglyphic features in Down syndrome that differed from controls were pointed out in 1939. In 1959, a chromosomal abnormality was proven to cause Down syndrome.

Pathophysiology: Three cytogenetic variants cause Down syndrome - trisomy 21, chromosomal translocation, and mosaicism.

Trisomy 21 accounts for nearly 95% of all cases. Most of the remaining cases have 46 chromosomes with translation of the long arm of an extra number 21 either to a D group or to another G group chromosome. As a woman ages, her risk of giving birth to a child with Down syndrome increases. This is of particular concern for women older than 35 years.

Less commonly, the patients with Down syndrome may have 46 chromosomes with either 21/22 or 21/21 translocation.

A few patients are mosaics with a normal cell line, usually milder physical stigmata, and impaired intelligence.

Frequency:

- **Internationally:** Down syndrome is the most common autosomal abnormality and occurs in approximately one per 700 live births. Down syndrome accounts for about one third of all moderate and severe mental handicaps in children of school age.

Mortality/Morbidity: About 25-30% of patients with Down syndrome die during the first year of life. The most frequent causes of death are respiratory infections (bronchopneumonia) and congenital heart disease. The life expectancy of patients with Down syndrome is a little reduced.

Race: Down syndrome has been reported in people of all races.

Sex: Both sexes are affected equally. Sexual incidence of patients with Down syndrome is the same. Males with Down syndrome are sterile. In the few affected females who have had children, about half of the offspring have been affected.

Age: Characteristic morphologic features of mongolism can be recognized immediately at the birth, but they are obvious in children older than one year. Some dermatologic features increase with advancing age.

History: The major features of Down syndrome are as follows:

- Mental retardation - Mild to severe, IQ = 25–50; constant feature
- Characteristic head appearance - A small head (brachycephaly), flat facies with increased interocular distance (hypertelorism), depressed nasal bridge, flat occiput, and broad short neck.
- Ocular anomalies - Narrow and upward and outward slating of the rima palpebrarum (in 80% of patients); white Brushfield spots arranged in concentric ring on the

periphery of the iris (in 60%), medial epicanthal folds, keratoconus, strabismus, cataracta (2%), and retinal detachment

- Oral features - Small mouth (relatively) with protrusion of the tongue (macroglossia) and difficulty in eating and speaking; scrotal tongue; hypoplasia of maxilla; delayed tooth eruption, hypodontia, juvenile periodontitis, cleft lip or palate (rare)
- Anomalous auricles - Small and misshapen ears with anomalies of the folds
- Skeletal anomalies - Short stature (below normal height); broad, short hands, feet, and digits; short curved fifth finger (dysplasia of the midphalanx), clinodactyly of the fifth finger; dysplasia of the pelvis (shallow acetabular angle with small iliac wings shown); joint laxity; a wide gap between the first and second toes; atlanto-occipital instability
- Muscle hypotonia in newborns with decreased response to normal stimuli
- Protuberant abdomen (with or without an umbilical hernia)
- Hypogenitalism (small penis, scrotum, and testes), hypospadia, cryptorchism; delayed and incomplete puberty (often)
- Congenital defects - Heart or endocardial cushion defects 40%, duodenal atresia, Hirschsprung disease, polydactylia and syndactylia
- Excess skin on the back of the neck
- Others - Recurrent respiratory infections, leukemia (1%), epilepsy (10%), hypothyroidism (3%), presenile dementia (development of Alzheimer disease after 40 years of age)
- Cutaneous manifestations of Down syndrome include the following:
    - Soft and velvety skin in early childhood.
    - Dry skin in late childhood - Xerosis (70%), atopic dermatitis (50%), palmoplantar hyperkeratosis (40-75%), seborrhoic dermatitis (31%)
    - Premature wrinkling of the skin; cutis marmorata; acrocyanosis
    - Bacteria infections; fungal infections (tinea); ectoparasitism (scabies)
    - Elastosis perforans serpiginosa
    - Syringomas
    - Alopecia areata (6%–8.9%)
    - Vitiligo
    - Angular cheilitis.

Physical: Xerosis, atopic dermatitis, secondary lichenification, seborrhoic dermatitis, and ichthyosiform changes are more frequent in childhood. The children have dry skin in early childhood. By the age of 15 years, more than 70% showed generalized xerosis of mild-to-moderate degree.

- Atopic dermatitis is present in more than 50% of patients in childhood. Its course often is complicated by lichenification and impetiginization, most likely caused by an increased susceptibility to infections.

- Patchy lichenification is present in approximately 30% of patients younger than 10 years and in more than 80% of patients older than 20 years.
    - This condition resembles lichen simplex and usually occurs on the upper arm, wrists, anterior thighs, posterior auricle, and posterior neck.
    - Seborrhoic dermatitis and ichthyosiform changes also have been described.
- Palmoplantar hyperkeratosis is not seen before the age of 5 months, but its incidence rose to 75% in children 5 years and older with normal vitamin A levels. A transverse palmar crease (simian crease) is seen in 40-50% of these patients.
- Skin ages prematurely, showing lentigines and atrophy.
- Vascular instability (acrocyanosis and cutis marmorata) is a frequent cutaneous manifestation of disease because peripheral circulation is poor and an increased incidence of congenital heart disease occurs. Cutis marmorata of the trunk and extremities in children is observed in 12.7% of patient with this syndrome.
- Systemic lupus erythematosus has been observed in patients with Down syndrome but the association is not convincing.
- Psoriasis runs its normal course in patients with Down syndrome, though a widespread, extremely hyperkeratotic form with lesions in unusual sites is observed.
- Carotenemia is no more frequent in patients with Down syndrome than in other persons with mental retardation.
    - Incidence is increased in cases associated with hypothyroidism.
    - Communal living, which often results in a diet rich in carotene products, is a reason for this condition.
- Calcinosis cutis associated with milialike syringomas also is observed in patients with Down syndrome with transepithelial elimination of calcium from tumors.
- Unusual forms of elastosis perforans serpiginosa are noted in patients with Down syndrome.
    - Onset of skin lesions is during the second decade of life.
    - Both sexes are affected with increased prevalence in males. (Male-to-female ratio is 4:1.)
    - Cutaneous lesions are more extensive and duration of the condition is longer – 10 years or more versus 5 years in the idiopathic type.
    - Keratotic papules often coalescence to form an arcuate or serpiginous pattern.
    - Lesions heal with atrophic scars.
- A variety of bacterial infections, fungi, or ectoparasite infestations afflict the patients with Down syndrome. Cutaneous bacterial infections (eg, angular cheilitis, folliculitis, furuncles, abscesses, secondary impetigo) are common in those patients with or without atopic dermatitis.
- Dermatophytic infections also are seen frequently in postpubertal institutionalized patients with this syndrome. The high prevalence of tinea pedis (>50% of affected patients) and increased incidence of severe onychomycosis in young adults result

from communal living.

- Pityrosporum folliculitis, a chronic persistent erythematous follicular papular eruption affecting the presternal and infrascapular region, is found in about 50% of affected men with this syndrome between the ages of 20 and 40 years but occurs uncommonly in affected women.
- Children with Down syndrome are predisposed to the development of crusted (Norwegian) scabies. The reasons for this propensity are unclear.
    - Patients have generalized erosions, scaling, and hyperkeratotic crusted plaques, especially on the flexural aspects of the wrists, buttocks, and sacrum.
    - Nails are deformed with marked subungual hyperkeratosis. Those patients have immunological dysfunction; importance is attached to poor cutaneous sensation leading to diminished likelihood of mites being mechanically removed.
- The tumor profile of patients with Down syndrome is different from that in other people.
- Syringomas occurred in patients with Down syndrome more often than in other patients.
    - These benign appendiceal tumors are observed in 18.5-39% of patients with this disease.
    - Females are affected more than twice as often as males.
    - Lesions usually are limited to regions around the eyes, but disseminated syringomas also are observed.
    - The presence of tumors is not related with the intelligence quotient or any other manifestation of disorder.
- Leukemia (acute and subacute) is 3 times more common in children with Down syndrome than in unaffected persons.
    - Leukemia cutis also is observed in these patients.
    - Congenital leukemia and leukemoid reactions, which are highly associated with trisomy 21, are difficult to distinguish on clinical and histologic grounds.
    - Recognition of a transient form of congenital leukemia is important for the treatment of such patients.
- Oral lesions of Down syndrome (fissured and geographic tongue, macroglossia, juvenile periodontitis) are frequent manifestations of the disease.
    - Fissuring and thickening of the lips and angular cheilitis are frequent and increase in incidence and severity with age.
    - Cheilitis occurs with greater frequency in children with Down syndrome than in unaffected persons.
    - It is explained by mechanical factors, trauma, actinic influence, atopy, avitaminosis, or low-grade infections (candidiasis).
- Fissured tongue (plicated or scrotal) occurs in up to 80% of children with Down syndrome but affects about 5% of the general population. It often is associated with

macroglossia. The cause of this condition is unclear.

- Geographic tongue is occurs in 11.3% of patients with this syndrome.
- Juvenile periodontitis is a feature of Down syndrome and its incidence among the various age groups parallels the occurrence of cheilitis but without significant correlation.

- Baby hair is normal at birth but often is fine and hypopigmented.
- Incidence of alopecia areata is higher than in dermatologic outpatients or in individuals with mental retardation. It varies between 6 and 8.9% of patients with this syndrome.
  - The disorder tends to be more severe, extensive, and persistent than in otherwise healthy patients with the condition.
  - A decrease in the T-cell-dependent immune response and immunoglobulin G (IgG) deficiencies is reported in these patients.

Causes:

- Three cytogenic variants cause Down syndrome.
  - Trisomy 21
  - Chromosomal translocation
  - Mosaicism
- The incidence of this syndrome at various maternal ages changes is as follows:
  - 15-29 years - 1:1500
  - 30-34 years - 1:800
  - 35-39 years – 1:270
  - 40-44 years - 1:100
  - Older than 45 years - 1:50
- On rare occasions, the disease can be observed in a few members of family.

DIFFERENTIALS Section 4 of 11 Back Top Next

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Pictures Bibliography

Other Problems to be Considered:

Cretinism

WORKUP Section 5 of 11 Back Top Next

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Pictures Bibliography

- Bhatt S, Schreck R, Graham JM, et al: Transient leukemia with trisomy 21: description of a case and review of the literature. Am J Med Genet 1995 Sep 25; 58(4): 310-4[Medline].
- Borgaonkar DS, Davis M, Bolling DR, Herr HM: Evaluation of dermal patterns in Down's syndrome by predictive discrimination. I. Preliminary analysis based on frequencies of patterns. Johns Hopkins Med J 1971 Mar; 128(3): 141-52[Medline].
- Desmons F, Bar J, Brandt A: Les signes cutanes du mongolisme (trisomie 21). Bull Soc fr Dermatol et Syphiligr 1973; 80: 233-7.
- Dourmishev A, Miteva L, Mitev V, et al: Cutaneous aspects of Down syndrome. Cutis 2000 Dec; 66(6): 420-4[Medline].
- Down JL: Observations on an ethnic classification of idiots. 1866. Ment Retard 1995 Feb; 33(1): 54-6[Medline].
- Ercis M, Balci S, Atakan N: Dermatological manifestations of 71 Down syndrome children admitted to a clinical genetics unit. Clin Genet 1996 Nov; 50(5): 317-20[Medline].
- Feingold M, Schneller S: Down syndrome and systemic lupus erythematosus. Clin Genet 1995 Nov; 48(5): 277[Medline].
- Lejeune J, Gautier M, Turpin R: Les chromosomes somatiques des enfants mongoliens. CR Acad Sci 1959; 248: 1721-22.
- Lerner LH, Wiss K, Gellis S, Barnhill R: An unusual pustular eruption in an infant with Down syndrome and a congenital leukemoid reaction. J Am Acad Dermatol 1996 Aug; 35(2 Pt 2): 330-3[Medline].
- Miller JR: Dermatoglyphics. J Invest Dermatol 1973 Jun; 60(6): 435-42[Medline].
- Reed TE, Borgaonkar DS, Conneally PM, et al: Dermatoglyphic nomogram for the diagnosis of Down's syndrome. J Pediatr 1970 Dec; 77(6): 1024-32[Medline].
- Rex AP, Preus M: A diagnostic index for Down syndrome. J.Pediatr 1982; 100: 903-6[Medline].
- Roizen NJ: Down syndrome: Progress in research. Ment Retard Dev Disabil Res Rev 2001 Feb; 7(1): 38-44.[Medline][Full Text].
- Satge D, Sommeler D, Geneix A, et al: A tumor profile in Down syndrome. Am. J.Med.Genet. 1998; 78: 207-16[Medline].
- Scherbenske JM, Benson PM, Totchford JP et al.: Cutaneous and ocular manifestations of Down syndrome. J.Am.Acad.Dermatol. 1990; 22: 933-38.[Medline].
- Scott JA, Wenger SL, Steele MW, Chakravarti A: Down syndrome consequent to a cryptic maternal 12p;21q chromosome translocation. Am J Med Genet 1995 Mar 13; 56(1): 67-71[Medline].
- Soares SR, Templado C, Blanco J, et al: Numerical chromosome abnormalities in the spermatozoa of the fathers of children with trisomy 21 of paternal origin: generalised tendency to meiotic non-disjunction. Hum Genet 2001 Feb; 108(2): 134-9[Medline][Full Text].
- Thomas L, Augey F, Chamchikh N, et al: [Cutaneous signs of trisomy 21]. Ann Dermatol Venereol 1994; 121(4): 346-50[Medline].
- Viner RM, Shimura N, Brown BD, et al: Down syndrome in association with features of the androgen insensitivity syndrome. J Med Genet 1996 Jul; 33(7): 574-7[Medline].
- Vintzileos AM, Egan JF: Adjusting the risk for trisomy 21 on the basis of second-trimester ultrasonography. Am J Obstet Gynecol 1995 Mar; 172(3): 837-44[Medline][Full Text].
- Wilms A, Dummer R: [Elastosis perforans serpiginosa in Down syndrome]. Hautarzt 1997 Dec; 48(12): 923-5[Medline].

Down Syndrome excerpt

Congestive Heart Failure and Pulmonary Edema

Last Updated: January 11, 2002

Synonyms and related keywords: CHF, pulmonary edema

Author: **Shamai Grossman, MD, MS**, Director, The Cardiac Emergency Center, Instructor, Department of Emergency Medicine, Harvard Medical School, Beth Israel Deaconess Hospital

Coauthor(s): **David FM Brown, MD**, Instructor, Department of Medicine, Division of Emergency Medicine, Harvard Medical School; Associate Chief, Department of Emergency Medicine, Massachusetts General Hospital

Shamai Grossman, MD, MS, is a member of the following medical societies: American College of Emergency Physicians

Editor(s): **William Chiang, MD**, Assistant Director, Assistant Professor of Clinical Surgery/Emergency Medicine, Department of Emergency Medicine, Bellevue Hospital Center; **Francisco Talavera, PharmD, PhD**, Senior Pharmacy Editor, Pharmacy, eMedicine; **Gary Setnik, MD**, Chair, Department of Emergency Medicine, Mount Auburn Hospital; Assistant Professor, Division of Emergency Medicine, Harvard Medical School; **John Halamka, MD**, Chief Information Officer, CareGroup Healthcare System, Assistant Professor of Medicine, Department of Emergency Medicine, Beth Israel Deaconess Medical Center; Assistant Professor of Medicine, Harvard Medical School; and **Barry Brenner, MD, PhD**, Chairman, Department of Emergency of Medicine, Professor, Departments of Emergency Medicine and Internal Medicine, University of Arkansas for Medical Sciences

Background: Congestive heart failure (CHF) is an imbalance in pump

Related Articles

Acute Respiratory Distress Syndrome

Altitude Illness - Pulmonary Syndromes

Anaphylaxis

Anemia, Acute

Bronchitis

Chronic Obstructive Pulmonary Disease and Emphysema

Dysbarism

Hyperventilation Syndrome

Myopathies

Pericarditis and Cardiac Tamponade

Pneumonia, Aspiration

Pneumonia, Bacterial

Pneumonia, Immunocompromised

Pneumonia, Mycoplasma

Pneumonia, Viral

Pneumothorax, Iatrogenic, Spontaneous and

function in which the heart fails to maintain the circulation of blood adequately. The most severe manifestation of CHF, pulmonary edema, develops when this imbalance causes an increase in lung fluid secondary to leakage from pulmonary capillaries into the interstitium and alveoli of the lung.

CHF can be categorized as forward or backward ventricular failure. Backward failure is secondary to elevated systemic venous pressure, while left ventricular failure is secondary to reduced forward flow into the aorta and systemic circulation. Furthermore, heart failure can be subdivided into systolic and diastolic dysfunction. Systolic dysfunction is characterized by a dilated left ventricle with impaired contractility, while diastolic dysfunction occurs in a normal or intact left ventricle with impaired ability to relax and receive as well as eject blood.

The New York Heart Association's functional classification of CHF is one of the most useful. Class I describes a patient who is not limited with normal physical activity by symptoms. Class II occurs when ordinary physical activity results in fatigue, dyspnea, or other symptoms. Class III is characterized by a marked limitation in normal physical activity. Class IV is defined by symptoms at rest or with any physical activity.

Pathophysiology: CHF is summarized best as an imbalance in Starling forces or an imbalance in the degree of end-diastolic fiber stretch proportional to the systolic mechanical work expended in an ensuing contraction. This imbalance may be characterized as a malfunction between the mechanisms that keep the interstitium and alveoli dry and the opposing forces that are responsible for fluid transfer to the interstitium.

Maintenance of plasma oncotic pressure (generally about 25 mm Hg) higher than pulmonary capillary pressure (about 7-12 mm Hg), maintenance of connective tissue and cellular barriers relatively impermeable to plasma proteins, and maintenance of an extensive lymphatic system are the mechanisms that keep the interstitium and alveoli dry.

Opposing forces responsible for fluid transfer to the interstitium include pulmonary capillary pressure and plasma oncotic pressure. Under normal circumstances, when fluid is transferred into the lung interstitium with increased lymphatic flow, no increase in interstitial volume occurs. When the capacity of lymphatic drainage is exceeded, however, liquid accumulates in the interstitial spaces surrounding the bronchioles and lung vasculature, thus creating CHF. When increased fluid and pressure cause tracking into the interstitial space around the alveoli and disruption of alveolar membrane junctions, fluid floods the alveoli and leads to pulmonary edema.

Etiologies of pulmonary edema may be placed in the following 6 categories:

1. Pulmonary edema secondary to altered capillary permeability: This category includes acute respiratory deficiency syndrome (ARDS),

Pneumomediastinum
Pulmonary Embolism
Shock, Septic
Venous Air Embolism

Continuing Education

CME available for this topic. Click here to take this CME.

Patient Education

Click here for patient education.

infectious causes, inhaled toxins, circulating exogenous toxins, vasoactive substances, disseminated intravascular coagulopathy (DIC), immunologic processes reactions, uremia, near drowning, and other aspirations.

2. Pulmonary edema secondary to increased pulmonary capillary pressure: This comprises cardiac causes and noncardiac causes, including pulmonary venous thrombosis, stenosis or veno-occlusive disease, and volume overload.

3. Pulmonary edema secondary to decreased oncotic pressure found with hypoalbuminemia

4. Pulmonary edema secondary to lymphatic insufficiency

5. Pulmonary edema secondary to large negative pleural pressure with increased end expiratory volume

6. Pulmonary edema secondary to mixed or unknown mechanisms including high altitude pulmonary edema (HAPE), neurogenic pulmonary edema, heroin or other overdoses, pulmonary embolism, eclampsia, postcardioversion, postanesthetic, postextubation, and post–cardiopulmonary bypass

This chapter is limited to cardiac causes of pulmonary edema and CHF and its relevant emergency care.

Frequency:

- **In the US:** More than 3 million people have CHF, and more than 400,000 new cases present yearly. Prevalence of CHF is 1-2% of the general population.

Mortality/Morbidity:

- Approximately 30-40% of patients with CHF are hospitalized every year. CHF is the leading diagnosis-related group (DRG) among hospitalized patients older than 65 years. The 5-year mortality after diagnosis was reported as 60% in men and 45% in women in 1971. In 1991, data from the Framingham heart study showed the 5-year mortality rate for CHF essentially remaining unchanged, with a median survival of 3.2 years for males and 5.4 years for females. This may be secondary to an aging US population with declining mortality due to other diseases.

- The most common cause of death is progressive heart failure, but sudden death may account for up to 45% of all deaths. After auditing data on 4606 patients hospitalized with CHF between 1992-1993, the total in-hospital mortality rate was 19%, with 30% of deaths occurring from noncardiac causes.

- Patients with coexisting insulin-dependent diabetes mellitus have a

significantly increased mortality rate.

Race:

- African Americans are 1.5 times more likely to die of CHF than whites. Nevertheless, African American patients appear to have similar or lower in-hospital mortality rates than white patients.

S x:

- Incidence is greater in males than in females for patients aged 40-75 years
- No sex predilection exists for patients older than 75 years

Age:

- Incidence of CHF increases with increasing age and affects about 10% of the population older than 75 years.

CLINICAL	Section 3 of 10 [Back Top Next]
Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Bibliography	

History:

- Anxiety
- Dyspnea at rest
- Dyspnea on exertion has been found to be the most sensitive complaint, yet the specificity for dyspnea is less than 60%.
- Orthopnea and paroxysmal nocturnal dyspnea (PND) are symptoms; however, sensitivity for orthopnea and PND is only 20-30%.
- Cough productive of pink, frothy sputum is highly suggestive of CHF.
- Edema
- Nonspecific complaints include the following:
    - Weakness
    - Lightheadedness
    - Abdominal pain
    - Malaise

- Wheezing
- Nausea

- Past medical history may include the following:
  - Cardiomyopathy
  - Valvular heart disease
  - Alcohol use
  - Hypertension
  - Angina
  - Prior myocardial infarction
  - Familial heart disease

Physical:

- Findings such as peripheral edema, jugular venous distention, and tachycardia are highly predictive of CHF. Overall specificity of physical examination has been reported at 90%; however, this same study reported a sensitivity of only 10-30%.
- Tachypnea, using accessory muscles of respiration
- Hypertension
- Pulsus alternans (alternating weak and strong pulse indicative of depressed left ventricle [LV] function)
- Skin may be diaphoretic or cold, gray, and cyanotic.
- Jugular venous distention (JVD) frequently is present.
- Wheezing or rales may be heard on lung auscultation.
- Apical impulse frequently is displaced laterally.
- Cardiac auscultation may reveal aortic or mitral valvular abnormalities, S_3 or S_4.
- Lower extremity edema also may be noted, especially in the subacute process.

Caus s:

- A variety of cardiac diseases cause CHF and pulmonary edema.

- The most common cause of heart failure is coronary artery disease, which is secondary to loss of left ventricular muscle, ongoing ischemia, or decreased diastolic ventricular compliance.
- Other disease processes include hypertension, valvular heart disease, congenital heart disease, other cardiomyopathies, myocarditis, and infectious endocarditis.
- CHF often is precipitated by cardiac ischemia or dysrhythmias, cardiac or extracardiac infection, pulmonary embolus, physical or environmental stresses, changes or noncompliance with medical therapy, dietary indiscretion, or iatrogenic volume overload.
- One also must consider systemic processes such as pregnancy and hyperthyroidism as precipitants of CHF.

DIFFERENTIALS	Section 4 of 10 [Back Top Next]
Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Bibliography	

Acute Respiratory Distress Syndrome
Altitude Illness - Pulmonary Syndromes
Anaphylaxis
Anemia, Acute
Bronchitis
Chronic Obstructive Pulmonary Disease and Emphysema
Dysbarism
Hyperventilation Syndrome
Myopathies
Pericarditis and Cardiac Tamponade
Pneumonia, Aspiration
Pneumonia, Bacterial
Pneumonia, Immunocompromised
Pneumonia, Mycoplasma
Pneumonia, Viral
Pneumothorax, Iatrogenic, Spontaneous and Pneumomediastinum
Pulmonary Embolism
Shock, Septic
Venous Air Embolism

Other Problems to be Considered:

The cardiac conditions combined with asthma or symptoms of chronic obstructive pulmonary disease (COPD) are difficult clinical challenges.

WORKUP	Section 5 of 10 [Back Top Next]
Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Bibliography	

Lab Studi s:

- Serum lab values may identify prerenal azotemia or elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin, suggestive of a congestive hepatopathy. Cardiac enzymes and other serum markers for ischemia or infarction may be useful as well.

- Arterial blood gas (ABG) may be of benefit in evaluation of hypoxemia, ventilation/perfusion (V/Q) mismatch, hypercapnia, and acidosis.

- Mild azotemia, decreased erythrocyte sedimentation rate (ESR), and proteinuria are observed in early and mild-to-moderate disease.

- Increased creatinine, hyperbilirubinemia, and dilutional hyponatremia are observed in severe cases.

Imaging Studies:

- Chest x-ray

    - Although diagnostic tests are of limited benefit in acute CHF, chest x-ray (CXR) is the most useful tool.

    - Cardiomegaly may be observed with a cardiothoracic ratio greater than 50%. Pleural effusions may be present bilaterally or, if they are unilateral, are more commonly observed on the right.

    - Early CHF may manifest as cephalization of pulmonary vessels, generally reflecting a pulmonary capillary wedge pressure (PCWP) of 12-18 mm Hg. As the interstitial fluid accumulates, more advanced CHF may be demonstrated by Kerley B lines (PCWP: 18-25 mm Hg).

    - Pulmonary edema is observed as perihilar infiltrates often in the classic butterfly pattern reflecting a PCWP greater than 25 mm Hg.

    - Several limitations exist to the use of chest x-rays when attempting to diagnose CHF. Classic radiographic progression often is not found, and as much as a 12-hour radiographic lag from onset of symptoms may occur. In addition, radiographic findings frequently persist for several days despite clinical recovery.

- Emergency transthoracic echocardiography

    - Emergency transthoracic echocardiography (ECHO) may help identify regional wall motion abnormalities as well as globally depressed or myopathic left ventricular function.

    - ECHO may help identify cardiac tamponade, pericardial constriction, and pulmonary embolus.

    - ECHO also is useful in identifying valvular heart disease, such as mitral or aortic stenosis or regurgitation.

Other Tests:

- Electrocardiogram (ECG) is a nonspecific tool but may be useful in diagnosing concomitant cardiac ischemia, prior myocardial infarction (MI), cardiac dysrhythmias, chronic hypertension, and other causes of left ventricular hypertrophy.

Procedures:

- No defined role exists for invasive monitoring devices such as central venous placement (CVP) lines. Time-consuming placement of pulmonary artery catheters has not been shown to prolong survival, even in the coronary care unit and, thus far, has not been well studied in the ED setting.

- Cardiac catheterization may be necessary for a complete evaluation and assessment of prognosis.

Prehospital Care:

- Prehospital notification by Emergency Medical Services (EMS) personnel should alert ED staff of a patient presenting with signs and symptoms of CHF and pulmonary edema. They should receive on-line medical advice for patients with high-risk presentations.

- Begin treatment with the ABCs. Administer supplemental oxygen, initially 100% nonrebreather facemask.

- Utilize cardiac monitoring and continuous pulse oximetry.

- Obtain intravenous access, as well as a prehospital ECG, if available.

- Provide nitroglycerin sublingual or spray for active chest pain in the patient without severe hypotension and IV furosemide.

Emergency Department Care:

- Begin ED management of a patient presenting with signs and symptoms of CHF and pulmonary edema with the ABCs. Administer supplemental oxygen, initially 100% nonrebreather facemask. Utilize cardiac monitoring and continuous pulse oximetry. Obtain IV access.

- To reduce venous return, elevate the head of the bed. Patients may be most comfortable in a sitting position with their legs dangling over the side of the bed, which allows for reduced venous return and decreased preload.

- Therapy generally starts with nitrates and diuretics if patients are hemodynamically stable. Many other treatment modalities may play some role in acute management.

- If possible, treat the underlying cause as well, if identified. This is particularly true for patients with known diastolic dysfunction who respond best to reductions in blood pressure, rather than to diuretics, nitrates, and inotropic agents.

- Eliminate contributing factors when possible.
- Restrict fluid and sodium.
- Consider other treatment modalities.
    - Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) - Recent data comparing nasal CPAP therapy and facemask ventilation therapy has demonstrated decreased need for intubation rates when these modalities are used. In patients with severe CHF treated with CPAP, however, no significant difference was found in short-term mortality and hospital stay. Although BiPAP therapy may improve ventilation and vital signs more rapidly then CPAP, a higher incidence of MI associated with BiPAP has been reported. BiPAP and CPAP are contraindicated in the presence of acute facial trauma, the absence of an intact airway, and in patients with an altered mental status or who are uncooperative.
    - Alternating tourniquets, formerly a mainstay of therapy, have been used to decrease preload. Their use has been supplanted by newer therapies such as intravenous nitroglycerin and nitroprusside.
    - Phlebotomy with removal of 500 cc of blood or via plasmapheresis is another former mainstay of therapy used to decrease preload. Its use has been supplanted by newer therapies such as intravenous nitroglycerin and nitroprusside.

Consultations:

- Cardiology
- Critical care services
- Cardiothoracic surgery for possible heart valve surgery or transplantation

The goal of pharmacotherapy is to achieve a PCWP of 15-18 mm Hg and a cardiac index >2.2 L/min/m^2, while maintaining adequate blood pressure and perfusion to essential organs. These goals may need to be modified for some patients.

Use of diuretics, nitrates, analgesics, and inotropic agents are indicated for the treatment of CHF and pulmonary edema. Calcium channel blockers, such as nifedipine and nondihydropyridines, increase mortality and increase incidence of recurrent CHF with chronic use. Conflicting evidence currently exists in favor, as well as against, the use of calcium channel blockers in the acute setting; at this time limit their acute use to patients with diastolic dysfunction and heart failure, a condition not easily determined in the ED.

Angiotensin converting enzyme (ACE) inhibitors, such as SL captopril or IV enalapril, may rapidly reverse hemodynamic instability and symptoms, possibly avoiding an otherwise

imminent intubation. Haude compared 25 mg of SL captopril with 0.8 mg of sublingual nitroglycerin in 24 patients with class III and class IV CHF and found that captopril induces a more sustained and more pronounced improvement in hemodynamics. Annane gave 1 mg of IV enalapril to 20 patients presenting with acute class III and class IV CHF over 2 hours and demonstrated rapid hemodynamic improvement with no significant adverse effects on cardiac output or hepatosplanchnic measurements.

Captopril may play a unique role in sustaining patients with renal failure and concomitant acute CHF while awaiting definitive therapy with dialysis. Since the information on this subject is still controversial and limited to small studies, their routine use cannot be recommended at this time. ACE inhibitors remain a promising area in need of further study.

Beta-blockers, possibly by restoring beta-1 receptor activity or via prevention of catecholamine activity, appear to be cardioprotective in patients with depressed left ventricular function. The US Carvedilol Heart Failure study group demonstrated a two-thirds decrease in mortality in patients taking carvedilol with left ventricular ejection fractions of 35% or less. Beta-blockers, particularly carvedilol, have been shown to improve symptoms in patients with moderate-to-severe heart failure. The role of beta-blockers in the acute setting, however, currently is unclear; limit use until hemodynamic studies indicate that further deterioration will not occur.

Because differentiating CHF and asthma exacerbations is often difficult, treating both with the shotgun approach often is employed, particularly as both may cause bronchospasm. Aerosolized beta-2 agonists, which are the more selective of beta-agonists, decrease tachycardia, dysrhythmias, and cardiac work while transiently enhancing cardiac function. Terbutaline has been shown to be successful in this setting, as well as albuterol, isoetharine, and bitolterol.

Limit roles of theophylline and aminophylline in the acute setting. They are positive inotropic agents mediated by an increase in catecholamines, and they dilate coronaries and exert mild diuretic effects. Nevertheless, they can exacerbate dysrhythmias (eg, multifocal atrial tachycardia [MAT], ischemia) by increasing cardiac work.

Steroids, IV or PO, have been shown to worsen preexisting heart failure due to systemic sodium retention and volume expansion, hypokalemia, and occasional hypertension. Inhaled steroids, due to their lack of systemic side effects, may be a reasonable option in this confusing patient presentation; however, given their delayed onset of action, they remain an area in need of further study.

Please see the chapter on Asthma for dosing schedules.

Drug Category: *Diuretics* -- First-line therapy generally includes a loop diuretic such as furosemide, which will inhibit sodium chloride reabsorption in the ascending loop of Henle.

Drug Name	Furosemide (Lasix) -- Administer loop diuretics IV, since this allows for both superior potency and higher peak concentration despite increased incidence of side effects, particularly ototoxicity.
Adult Dose	A reasonable approach for furosemide might be as follows: 10-20 mg IV for patients symptomatic with CHF not already using diuretics 40-80 mg IV for patients already using diuretics 80-120 mg IV for patients whose symptoms are refractory to

	the initial dose after 1 h of its administration Higher doses and more rapid redosing may be appropriate for the patient in severe distress
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; hepatic coma; anuria; severe electrolyte depletion
Interactions	Metformin decreases concentrations; interferes with hypoglycemic effect of antidiabetic agents and antagonizes muscle relaxing effect of tubocurarine; auditory toxicity appears to be increased with coadministration of aminoglycosides; hearing loss of varying degrees may occur; anticoagulant activity of warfarin may be enhanced when taken concurrently; increased plasma lithium levels and toxicity are possible when taken concurrently
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Perform frequent serum electrolyte, carbon dioxide, glucose, creatinine, uric acid, calcium, and BUN determinations during first few months of therapy and periodically thereafter
Drug Name	Metolazone (Mykrox, Zaroxolyn) -- Both chlorothiazide and metolazone have been used as adjunctive therapy in patients initially refractory to furosemide. Chlorothiazide, however, at doses of 250-500 mg IV, decreases GFR with CHF and, thus, is less potent and causes a greater loss of potassium. Conversely, metolazone has been demonstrated to be synergistic with loop diuretics in treating refractory patients.
Adult Dose	5-10 mg PO before redosing with furosemide
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; hepatic coma; encephalopathy; anuria
Interactions	Thiazides may decrease effect of anticoagulants, sulfonylureas, and gout treatments; anticholinergics and amphotericin B may increase toxicity of thiazides; effects of thiazides may decrease when used concurrently with bile acid sequestrants, NSAIDs, or methenamine; when administered concurrently, thiazides increase toxicity of anesthetics, diazoxide, digitoxin, lithium, loop diuretics, antineoplastics, allopurinol, calcium salts, vitamin D, and nondepolarizing muscle relaxants
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Pr cautions	Caution in hepatic or renal disease, diabetes mellitus, gout, or lupus erythematosus

Drug Category: *Nitrates* -- Reduce myocardial oxygen demand by lowering preload and afterload.

In severely hypertensive patients, nitroprusside causes more arterial dilatation than nitroglycerin. Nevertheless, due to thiocyanate toxicity and the coronary steal phenomenon associated with nitroprusside, IV nitroglycerin is still the therapy of choice for afterload

reduction.

Drug Name	Nitroglycerin (Nitro-Bid, Nitrol, Nitrostat) -- SL nitroglycerin and nitrospray are particularly useful in the patient who presents with acute pulmonary edema with a systolic blood pressure of at least 100 mm Hg. Similar to SL, nitrospray's onset is 1-3 min with a half-life of 5 min. Applicability of nitrospray may be easier, and storage is up to 4 y. One study demonstrated significant and rapid hemodynamic improvement in 20 patients given nitrospray with pulmonary edema in an ICU setting. Topical nitrate therapy is reasonable in a patient presenting with class I to II CHF. However, in patients with more severe signs of heart failure or pulmonary edema, IV nitroglycerin is preferred since it is easier to monitor hemodynamics and absorption, particularly in the diaphoretic patient. Oral nitrates, due to delayed absorption, have little role in the acute presentations of CHF.
Adult Dose	Nitrospray: single spray (0.4 mg) equivalent to a single 1/150 SL; may repeat q3-5min as hemodynamics permit, up to a maximum of 1.2 mg Ointment: Apply 1-2 inches of nitropaste to chest wall Injection: start at 20 mcg/min IV and rate to effect in 5-10 mcg increments q3-5min
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; severe anemia; shock; postural hypotension; head trauma; closed-angle glaucoma; cerebral hemorrhage
Interactions	Aspirin may increase nitrate serum concentrations; marked symptomatic orthostatic hypotension may occur with coadministration of calcium channel blockers (dose adjustment of either agent may be necessary)
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Exercise caution with coronary artery disease and low systolic blood pressure.
Drug Name	Nitroprusside sodium (Nitropress) -- Produces vasodilation and increases inotropic activity of the heart. At higher dosages may exacerbate myocardial ischemia by increasing heart rate. Easily titratable.
Adult Dose	10-15 mcg/min and titrate to effective dose range of 30-50 mcg/min and a systolic blood pressure of at least 90 mm Hg
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; subaortic stenosis; optic atrophy; tobacco amblyopia; idiopathic hypertrophic; atrial fibrillation or flutter
Interactions	Patients receiving other hypertensive therapy may be more sensitive to sodium nitroprusside
Pregnancy	C - Safety for use during pregnancy has not been established.

Pr cauti ns	Caution in increased intracranial pressure, hepatic failure, severe renal impairment, and hypothyroidism; in renal or hepatic insufficiency, nitroprusside levels may increase and can cause cyanide toxicity; sodium nitroprusside has the ability to lower blood pressure and thus should be used only in those patients with mean arterial pressures >70 mm Hg

Drug Category: *Analgesics* -- Morphine IV is an excellent adjunct in acute therapy. In addition to being both an anxiolytic and an analgesic, its most important effect is venodilation, which reduces preload. Also causes arterial dilatation, which reduces systemic vascular resistance (SVR) and increases cardiac output. Narcan also can reverse the effects of morphine. However, some evidence indicates that morphine use in acute pulmonary edema may increase the intubation rate.

Drug Name	Morphine sulfate (Duramorph, Astramorph, MS Contin) -- DOC for narcotic analgesia due to reliable and predictable effects, safety profile, and ease of reversibility with naloxone. Morphine sulfate administered IV may be dosed in a number of ways and commonly is titrated until desired effect is obtained.
Adult Dose	2-5 mg IV and repeated q10-15min unless respiratory rate is <20 breaths/min or systolic blood pressure is <100 mm Hg
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; hypotension; potentially compromised airway with uncertain rapid airway control; respiratory depression; nausea; emesis; constipation; urinary retention
Interactions	Phenothiazines may antagonize analgesic effects of opiate agonists; tricyclic antidepressants, MAOIs, and other CNS depressants may potentiate adverse effects of morphine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in atrial flutter and other supraventricular tachycardias; has vagolytic action and may increase ventricular response rate

Drug Category: *Inotropic agents* -- Principal inotropic agents include dopamine, dobutamine, inamrinone (formerly amrinone), milrinone, dopexamine, and digoxin. In the hypotensive patient presenting with CHF, dopamine and dobutamine are agents usually employed. Inamrinone or milrinone inhibits phosphodiesterase, resulting in an increase of intracellular cyclic AMP and alteration in calcium transport. As a result, they increase cardiac contractility and reduce vascular tone by vasodilatation.

Dopexamine is a new synthetic catecholamine with beta-2 and dopaminergic properties causing vasodilation and increased inotropism but with tachycardia as well. Ultimately may have a role as an emergent inotropic agent, but dobutamine is probably the current agent of choice.

Digoxin has no role in the emergency management of CHF due to delayed absorption and diminished efficacy at times of increased sympathetic tone. Thus, has little, if any, benefit in the patient presenting concomitantly with atrial fibrillation and rapid ventricular response. Limit use of digoxin to chronic CHF in which its role has been well established.

	Dopamine (Intropin) -- Stimulates both adrenergic and

Drug Name	dopaminergic receptors. Hemodynamic effects depend on the dose. Lower doses stimulate mainly dopaminergic receptors that produce renal and mesenteric vasodilation. Cardiac stimulation and renal vasodilation is produced by higher doses. Positive inotropic agent at 2-10 mcg that can lead to tachycardia, ischemia, and dysrhythmias. Doses >10 mcg cause vasoconstriction, which increases afterload.
Adult Dose	5 mcg/kg/min and increase at 5 mcg/kg/min increments to a 20 mcg/kg/min dose
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; pheochromocytoma; ventricular fibrillation
Interactions	Phenytoin, alpha- and beta-adrenergic blockers, general anesthesia, and MAOIs increase and prolong effects of dopamine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Monitor closely urine flow, cardiac output, pulmonary wedge pressure, and blood pressure during the infusion; prior to infusion, correct hypovolemia with either whole blood or plasma, as indicated; monitoring central venous pressure or left ventricular filling pressure may be helpful in detecting and treating hypovolemia

Drug Name	Dobutamine (Dobutrex) -- Produces vasodilation and increases inotropic state. At higher dosages may cause increased heart rate, thus exacerbating myocardial ischemia. Strong inotropic agent with minimal chronotropic effect and no vasoconstriction.
Adult Dose	Starting dose: 2.5 mcg/kg/min IV; generally therapeutic in the range of 10-40 mcg/kg/min
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; idiopathic hypertrophic subaortic stenosis; atrial fibrillation or flutter
Interactions	Beta-adrenergic blockers antagonize effects of dobutamine; general anesthetics may increase toxicity
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Following a myocardial infarction use with extreme caution; hypovolemic state should be corrected before using this drug

Drug Category: *Human B-type natriuretic peptides* -- Dilate veins and arteries.

Drug Name	Nesiritide (Natrecor) -- Recombinant DNA form of human B-type natriuretic peptides (hBNP), which dilate veins and arteries. Human BNP binds to particulate guanylate cyclase receptor of vascular smooth muscle and endothelial cells. Binding to receptor causes increase in cyclic GMP, which serves as second messenger to dilate veins and arteries. Reduces pulmonary capillary wedge pressure and improves dyspnea in

	patients with acutely decompensated congestive heart failure.
Adult Dose	2 mcg/kg IV bolus over 60 s; follow by 0.01 mcg/kg/min continuous infusion; bolus volume (mL) = 0.33 X patient weight (kg); infusion flow rate of bolus (mL/h) = 0.1 X patient wt (kg)
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; systolic blood pressure <90 mm Hg; patients suspected of having, or known to have, low cardiac filling pressures, significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, conditions in which cardiac output is dependent upon venous return
Interactions	Concurrent administration with ACE inhibitors and other vasodilators may cause hypotension
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Do not initiate at dose higher than recommended; may affect renal function in patients whose renal function may depend on activity of renin-angiotensin-aldosterone system; may cause hypotension (administer in settings where blood pressure can be monitored closely); discontinue drug if hypotension develops; ventricular tachycardia, non-sustained VT, headache, abdominal pain, back pain, insomnia, anxiety, angina pectoris, nausea, and vomiting may occur

FOLLOW-UP Section 8 of 10 [Back Top Next]

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Bibliography

Further Inpatient Care:

- Depending on the response to initial ED therapy, disposition decisions vary.
    - With few exceptions, patients presenting with acute symptoms of CHF or pulmonary edema require hospital admission. Many patients, however, who respond rapidly to early therapy may require only standard hospital ward admission with telemetry monitoring if ischemic etiologies are being considered.
    - Some criteria for discharge from the ED would include gradual onset of shortness of breath, rapid response to therapy, oxygen saturation greater than 90%, and acute coronary syndromes and MI unlikely as the precipitating event.
    - Those patients who require intubation or remain with significant respiratory, hemodynamic, and/or cardiovascular compromise often require ICU or CCU admission.
    - If left ventricular function has not been well established previously, obtain either a multigated nuclear imaging (MUGA) scan or an echocardiogram, which enables assessment of valvular function and wall motion abnormalities as well as ejection fraction.

- In patients refractory to medical therapy or with evidence of cardiogenic shock, cardiac catheterization, angioplasty, coronary bypass, or intraaortic balloon pump (IABP) may be helpful.

Further Outpatient Care:

- Center outpatient care around patient education with specific instructions regarding dietary restrictions and compliance with medical therapy.

In/Out Patient Meds:

- ACE inhibitors are indicated in patients with ejection fractions of 35% or less.
- Digoxin also may be helpful in patients with ejection fractions of 35% or less.
- Diuretics, such as furosemide, may be helpful regardless of ejection fraction.
- Beta-blockers appear to be cardioprotective in patients with depressed left ventricular function. The US carvedilol heart failure study group demonstrated a two-thirds decrease in mortality in patients taking carvedilol with left ventricular ejection fractions of 35%. Beta-blockers are indicated as therapy for patients with diastolic dysfunction or for patients with coronary insufficiency.
- Calcium channel blockers, such as nifedipine and nondihydropyridines, increase mortality rates and incidence of recurrent CHF with chronic use in patients with depressed LV function. Amlodipine is the exception to this rule. Calcium channel blockers are useful in patients with diastolic dysfunction and heart failure.

Transfer:

- Consider transfer for unstable patients being evaluated in a center without access to cardiac catheterization or IABP. These patients might include the following:
  - Those who are refractory to medical therapy
  - Those in cardiogenic shock
  - Those with significant aortic stenosis or other valvular abnormalities possibly requiring surgical intervention or valvuloplasty

Deterrence/Prevention:

- Emphasize patient education with intense instruction regarding compliance with dietary restrictions and medical therapy.
- Emphasize close monitoring of blood pressure, particularly in patients with diastolic dysfunction.
- Patient should modify diet as follows:
  - Sodium restriction (initially 4 g/d)

- Weight reduction (if appropriate)
- Appropriate fluid restriction

- Patient should modify activity as follows:
  - During severe stage, bed rest with elevation of head of bed and anti-embolism stockings to help control leg edema
  - Gradual increase in activity with walking to help increase strength

Complications:

- Acute MI
- Cardiogenic shock
- Arrhythmias (most commonly atrial fibrillation)
- Ventricular arrhythmias, such as ventricular tachycardia, often are seen in patients with significantly depressed left ventricular function.
- Electrolyte disturbances
- Mesenteric insufficiency
- Protein enteropathy
- Digitalis intoxication

Prognosis:

- Based on data from 4606 patients hospitalized with CHF between 1992-1993, total in-hospital mortality was 19%, with 30% of deaths occurring from noncardiac causes. These patients, however, were noted to have had suboptimal use of proven efficacious therapy, compared with those who survived hospitalizations, particularly among women and the elderly. Thirty-year data from the Framingham heart study demonstrated a median survival of 3.2 years for males and 5.4 years for females.
- Results of initial treatment usually are good, regardless of cause.
- Long-term prognosis is variable. Mortality rates range from 10% in patients with mild symptoms to 50% with advanced, progressive symptoms.

Patient Education:

- Provide instructions to patients discharged home to return to the ED for recurrence or changes in severity of symptoms.
- Provide specific instructions to patients discharged regarding dietary restrictions and compliance with medical therapy.

- Require patients to promptly follow up with their primary care physician or cardiologist.
- Advise patients that printed information is available from the following organizations:
  - American Heart Association, 1615 Stemmons Freeway, Dallas, TX 75207, (214) 748-7212
  - American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814, (301) 897-5400

MISCELLANEOUS	Section 9 of 10 [Back Top Next]

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Bibliography

M dical/Legal Pitfalls:

- Failure to recognize and initiate early management of a patient presenting with signs and symptoms of CHF and pulmonary edema is a pitfall because therapy must begin with the ABCs, and early treatment should include nitrates and diuretics, if hemodynamics are stable.
- Failure to obtain an ECG early is a pitfall because this may be useful in diagnosing dysrhythmias, concomitant cardiac ischemia, or prior MI; early ECG also is helpful in differentiating CHF from other etiologies. Remember, the most common cause of CHF is coronary artery disease.
- Failure to consider use of both CPAP and BiPAP early in therapy as a means to decrease need for intubation and improve acute respiratory status
- Failure to consider and evaluate for diseases with similar presentations
- Failure to educate patients concerning changes or noncompliance with medical therapy and dietary restrictions to help prevent further recurrence
- Discharging patients who may have had acute MI as a cause of CHF

BIBLIOGRAPHY	Section 10 of 10 [Back Top

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Bibliography

- Edwards JD, Grant PT, Plunkett P: The hemodynamic effects of sublingual nitroglycerin spray in severe left ventricular failure. Intensive Care Med 1989; 15: 247-249[Medline].
- Gordon HS, Harper DL, Rosenthal GE: Racial variation in predicted and observed in-hospital death: A regional analysis. JAMA 1996; 276: 1639-1644[Medline].
- Hamilton RJ, Carter W, Galahger EJ: Rapid improvement of acute pulmonary edema with sublingual captopril. Academic Emergency Medicine 1996; 3: 205-212[Medline].
- Harlan W, Oberman A, Grimm R: Chronic congestive heart failure in coronary artery disease: Clinical criteria. Ann Intern Med 1977; 86: 133-138[Medline].
- Lin M: Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema. Chest 1995; 107: 1379-1386[Medline].
- Melandri G, Semprini F, Branzi A: Comparative hemodynamic effects of transdermal vs

intravenous nitroglycerin in acute myocardial infarction with elevated pulmonary artery pressure. Eur Heart J 1990; 649-655[Medline].

- Polese A, Fiorenti C, Olivari MT: Clinical use of nifedipine in acute pulmonary edema. Am J Med 1979; 66: 825-830[Medline].
- Andersson B, Waagstein F: Spectrum and outcome of congestive heart failure in a hospitalized population. Am Heart J 1993 Sep; 126(3 Pt 1): 632-40[Medline].
- Annane D, Bellissant E, Pussard E: Placebo-controlled, randomized, double-blind study of intravenous enalaprilat efficacy and safety in acute cardiogenic pulmonary edema. Circulation 1996 Sep 15; 94(6): 1316-24[Medline].
- Chen JT: Radiographic diagnosis of heart failure. Heart Dis Stroke 1992 Mar-Apr; 1(2): 58-63[Medline].
- Clinical Quality Improvement Network Investigators: Mortality risk and patterns of practice in 4606 acute care patients with congestive heart failure. The relative importance of age, sex, and medical therapy. Arch Intern Med 1996 Aug 12-26; 156(15): 1669-73[Medline].
- Connors AF, Jr, Speroff T, Dawson NV: The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996; 276: 889-897[Medline].
- Goldstein RE, Boccuzzi SJ, Cruess D: Diltiazem increases late onset congestive heart failure in post myocardial infarction patients with early reduction in ejection fraction. Circulation 1991; 83: 52-60[Medline].
- Kannel WB, Pinsky JL: Trends in cardiac failure incidence and causes of three decades in the Framingham study. J Am Coll Cardiol 1991; 17: 87A.
- Kiyingi A, Field MJ, Pawsey CC: Metalozone in treatment of severe refractory congestive cardiac failure. Lancet 1990; 335: 29-31[Medline].
- Kostuk W, Barr JW, Simon AL: Correlations between the chest film and hemodynamics in acute myocardial infarction. Circulation 1973; 48: 624-632[Medline].
- Massie BM: Congestive heart failure: Current controversies and future prospects. Am J Cardiol 1990.
- Mehta S, Jay GD, Woolard RH: Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. Crit Care Med 1997 Apr; 25(4): 620-8 [Medline].
- Parmley WW: Pathophysiology and current therapy of congestive heart failure. J Am Coll Cardiol 1989 Mar 15; 13(4): 771-85[Medline].